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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,724	LOSCALZO ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response and amendments filed 17 October 2006 to the Office Action mailed 17 July 2006 is acknowledged and entered.

2. In view of remarks and amendment filed 17 October 2006, the following rejections in the Office Action mailed 17 July 2006 are hereby withdrawn under:

- 35 U.S.C. §112, first paragraph to Claims 1-11 and 21-22; and
- 35 U.S.C. § 103(a) to Claims 1-10 and 21-22.

3. The Art Unit Location for your application under prosecution at the United States Patent and Trademark Office (i.e., USPTO) has been changed to Art Unit 1657. To aid in correlating any papers for this application (i.e., 10/692,724), all further correspondence regarding this application should be directed to Examiner Kailash C. Srivastava in Art Unit 1657.

CLAIMS STATUS

4. Claims 11-20 and 23-37 have been cancelled.

5. Claims 1 and 7-8 have been amended.

6. Claims 1-10 and 21-22 are pending and are examined on merits.

Priority

7. Claim for domestic priority under 35 U.S.C. §119(e) to Provisional U.S. Applications 60/162,230 and 60/179,020 filed on 10/29/1999 and 1/31/2000 respectively is acknowledged.

8. Claim for domestic priority under 35 U.S.C.§121 to Non-provisional U.S. applications 09/697,317 filed 10/27/2000, now U.S. Patent 6,635,273 and 10/679,257 filed 10/07/2003 is acknowledged.

9. The disclosures and Claims presented in all the priority Applications cited in items 7-8 *supra*, have been carefully and fully reviewed. The information presented in U.S. Provisional Application Serial Number 60/162,230 is not consistent with the subject matter presented in the disclosure and elected claims for the U.S. Non-Provisional Application Number 10/692,724 currently under prosecution. Accordingly, the benefit of priority to instant U.S. Non-provisional Application Serial Number

10/692,724 is granted to the filing date of 1/31/2000 that is the filing date of U.S. Provisional Application Serial Number 60/179,020 filed 1/31/2000.

Information Disclosure Statement

10. The Information Disclosure Statement (i.e., IDS) filed 17 October 2006 has been made of record, considered and duly initialed sheets 1-5 of the PTO/SB/08A are enclosed with this Office Action.

Objection To Claims

- Claim 1 is objected to because of the phrase "therapeutically effective amount". Since in the claimed invention a particular dose or a range of dose (e.g., 250 mg/day) is imperative to clear understanding of the claimed method of treatment for the claimed disease, recitation of a given dose is important to the invention.

All other claims depend directly or indirectly from the rejected claims (e.g., Claim 1) and are, therefore, also objected for the reasons set forth above.

Claim Rejections - 35 U.S.C. §112

11. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

12. Claims 1-10 and 21-22 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession; at the time the invention was made, of the specific subject matter claimed. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude, "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T] he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such

descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. *In* Regents of the University of California v. Eli Lilly & Co. the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or sub-combinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.
>
> MPEP §2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP §2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what does not constitute a representative number of species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are:(1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." (MPEP §2163).

In the instant case, the claims are drawn to "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one nitrosated angiotensin converting enzyme inhibitor" (i.e., NACEI), "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like. Said NACEI further comprises a pharmaceutical acceptable carrier and may also be a salt of a NACEI. Said NACEI is administered in a solid dose form of a capsule or tablet, wherein said tablet or capsule is a sustained release capsule or tablet.

The claimed invention is assessed as follows with regard to the written description factors listed *supra*.

(a) Level of skill and knowledge in the art:

At least a Bachelor Degree in Biochemical engineering, Biochemistry, Biology, Biophysics, Chemical engineering, Chemistry, Civil engineering, Environmental engineering, Environmental Science, Hydraulics, Microbiology, Molecular biology, or Pharmacology.

(b) Partial structure:

The detailed description in specification despite giving a detailed list of angiotensin converting enzyme inhibitor (i.e., ACEI), or other nitrosated salts to treat nitric oxide insufficiency-mediated vascular/cardiovascular diseases (See, e.g., Page 28, Lines 28-30; Page 30, Lines 5-12) does not clearly detail which are the NACEI or salts thereof (See e.g., Page 1, Lines 14-30; Page 3, Lines 15-30). The only description is that a patient in need thereof is administered at least one NACEI and the claims (see Claim 1) name a number of NACEIs.

(c) Physical and/or chemical properties:

The physical and chemical properties of the precursors for the NACEIS, but for the claimed NACEIs are not described in the specification. If such a showing exists in the specification as currently presented, it should be clearly made of record.

(d) Functional characteristics:

Except to state that the at least one NACEI is applicable to treat the nitric oxide insufficiency-mediated vascular/cardiovascular diseases and giving a detailed description of all different cardiovascular/vascular diseases, the disclosure as currently presented does not present any structure function relationship for said at least one NASEI or salts thereof (See, e.g., Specification, Page 1, Lines 17-22).

(e) Method of making the claimed invention:

Despite providing a limited guidance to demonstrate claimed invention and to state that the claimed NASEIs are administered to a patient in need thereof to treat cardiovascular disease (e.g., hypertension) the description of the invention as currently presented in Pages 1-41 and accompanying figures and data table does not clearly and

concisely demonstrate a method to treat a cardiovascular disease (e.g., hypertension, congestive heart failure, myocardial infarction, artheriosclerosis) through administration of a NASEI or a salt thereof further comprising a pharmaceutically acceptable carrier in a solid dose form, wherein said solid dose form is a sustained-release dose. In the absence of said written descriptions, at the time of filing instant application and claiming the claimed invention as presented in the specification, it is not affirmative that the applicants indeed have the possession of the claimed invention as claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the claims because Claim 1 is the generic claim, and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

13. Claims 1-10 and 21-22 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one nitrosated angiotensin converting enzyme inhibitor" (i.e., NACEI), "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like. Said NACEI further comprises a pharmaceutical acceptable carrier and may also be a salt of a NACEI. Said NACEI is administered in a solid dose form of a capsule or tablet, wherein said tablet or capsule is a sustained release capsule or tablet.

From the record of the present disclosure, however, the information as currently presented in Pages 1-41 and accompanying figures and data table does not clearly and concisely demonstrate a method to treat a cardiovascular disease (e.g., hypertension, congestive heart failure, myocardial infarction, artheriosclerosis) by administering a NASEI or a salt thereof further comprising a pharmaceutically acceptable carrier in a solid dose form, wherein said solid dose form is a sustained-release dose

Thus, specification as currently presented while enabling treatment of a vascular/ cardiovascular disease via administering an angiotensin converting enzyme inhibitor or a nitrosated compound that is not an angiotensin converting enzyme inhibitor to a patient in need thereof, does not give adequate disclosure

for a person of skill to practice the claimed invention, wherein the claimed NASEI as a solid dose in form of a sustained release tablet or capsule has been administered to a patient in need thereof to treat a vascular, or a cardiovascular disease. Therefore, as currently presented, the specification does not provide for one of ordinary skill to practice the invention as claimed.

A person of ordinary skill would not be able to practice the invention because undue experimentation will be required to obtain "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one " NACEI, or salt thereof, "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like, wherein said NACEI further comprises a pharmaceutically acceptable carrier due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated below.

a. *Quantity of Necessary Experimentation*

Since the specification does not provide any evidence on how the claimed NASEI is obtained and how much of a solid dose of said NASEI should be administered to a patient in need thereof, an artisan of ordinary skill will have to perform a number of permutations and combinations to obtain a range of dose for the patient population to be administered said compound according to claimed invention. This is because the dosage is a function of at least age/weight among other parameters of a given patient population.

b. *Limited Amount of Guidance*

The specification as currently presented does not provide a clear-cut guidance to obtain the claimed invention method to treat a nitric oxide insufficiency mediated vascular/ cardiovascular disease in a patient via administering to said patient a solid dose in the form of a tablet or capsule of a NASEI.

c. *Limited Number of Working Examples in the Specification*

The specification does not provide any specific example to practice the claimed invention of specifically administering a solid dose in the form of a tablet or capsule of a NASEI to a patient having a nitric oxide insufficiency mediated vascular/ cardiovascular disease.

d. *Nature of the Invention*

The currently presented specification does not delineate the claimed method of making the claimed NASE, nor does it demonstrate administering a solid dose in the form of a tablet or capsule of a NASEI to a patient having a nitric oxide insufficiency mediated vascular/ cardiovascular disease to treat said vascular/cardiovascular disease in a patient.

e. *State of the Prior Art*

The prior art description in the specification is adequate regarding treating a nitric oxide insufficiency mediated vascular/ cardiovascular disease via administering a nitrosated compound other than a NASEI.

f. *Relative Skill Level of those in the Art*

At least a Bachelor Degree in Biochemical engineering, Biochemistry, Biology, Biophysics, Chemical engineering, Chemistry, Civil engineering, Environmental engineering, Environmental Science, Hydraulics, Microbiology, Molecular biology, or Pharmacology.

g. *Predictability or Unpredictability in the Art*

Unless supported with illustrative experimental evidence, biological responses are unpredictable. Thus, information obtained under one set of detrimental parameters may not be extrapolated for another set of parameters/environmental or specific conditions.

h. *Breadth of the Claims*

The claimed invention is drawn upon claims that are not supported by the presently detailed specification.

14. Claims 1-10 and 21-22 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with those claims. The claims are drawn to "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one nitrosated angiotensin converting enzyme inhibitor" (i.e., NACEI), "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like. Said NACEI further comprises a pharmaceutical acceptable carrier

and may also be a salt of a NACEI. Said NACEI is administered in a solid dose form of a capsule or tablet, wherein said tablet or capsule is a sustained release capsule or tablet.

From the record of the present disclosure, however, the information as currently presented in Pages 1-41 and accompanying figures and data table does not clearly and concisely demonstrate a method to treat a cardiovascular disease (e.g., hypertension, congestive heart failure, myocardial infarction, artheriosclerosis) by administering a NASEI or a salt thereof further comprising a pharmaceutically acceptable carrier in a solid dose form, wherein said solid dose form is a sustained-release dose

Thus, specification as currently presented while enabling treatment of a vascular/ cardiovascular disease via administering an angiotensin converting enzyme inhibitor or a nitrosated compound that is not an angiotensin converting enzyme inhibitor to a patient in need thereof, does not give adequate disclosure for a person of skill to practice the claimed invention, wherein the claimed NASEI as a solid dose in form of a sustained release tablet or capsule has been administered to a patient in need thereof to treat a vascular, or a cardiovascular disease. Therefore, as currently presented, the specification does not provide for one of ordinary skill to practice the invention as claimed.

A person of ordinary skill would not be able to practice the invention because undue experimentation will be required to obtain "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one " NACEI, or salt thereof, "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like, wherein said NACEI further comprises a pharmaceutically acceptable carrier due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated above.

15. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

16. Claims 1-10 and 21-22 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The recitation, "characterized by" at Claim 1, Line 2 renders that claim unclear, vague and difficult to comprehend because it is not clear whether said recitation encompasses other ingredients, like the conventional term " comprising", or whether said recitation excludes other ingredients like the conventional term "consisting of". Said recitation will be read as including other ingredients. Suggestion is, e.g., the term " having".

- Claim 21 as currently presented encompasses the subject matter already claimed in claim 1 or in claims 1, 3 and 7 combined together. Therefore, Claim 21 does not further limit the subject matter claimed in Claims 1, 3 and 7. Appropriate correction is required.

- In Claim 22, the limitations "a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture of two or more thereof" lacks sufficient antecedent basis because Claim 22 depends from Claim 21, Claim 21 depends from Claim 1. Neither Claim 21, nor Currently Amended Claim 1 recite the limitations "a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture of two or more thereof". Appropriate correction is required.

All other claims depend directly from the rejected claims (e.g., 1) and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 102/103

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

18. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § ***102***(f) or (g) prior art under 35 U.S.C.§ 103(a).

20. Claims 1-10 and 21-22 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Del Soldato (WO 99/00361) which is equivalent of Del Soldato (U.S. Patent 218, 417 B1). In this rejection U.S. Patent 218, 417 B1 is discussed.

Claims recite "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one nitrosated angiotensin converting enzyme inhibitor" (i.e., NACEI), "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like. Said NACEI further comprises a pharmaceutical acceptable carrier and may also be a salt of a NACEI. Said NACEI is administered in a solid dose form of a capsule or tablet, wherein said tablet or capsule is a sustained release capsule or tablet.

Regarding Claims 1-9 and 21-22, Del Soldato teaches a method to treat a cardiovascular disease (e.g., hypertension, congestive heart failure or angina) in an individual comprising administering to said individual an effective amount of one or more nitrate salts of ACE inhibitors and a pharmaceutically acceptable excipient or carrier comprising (See Column 6, Lines 10-67), e.g., Enalapril, Imidapril, Perinodopril, Ramipril or Spirapril, residues Column 7, Lines 1-19; Column 8, Lines 1-13 and Lines 18-27) in a solid dosage form (Column 4, Lines 40-60). Note that dosage shown in Table within the body of Example 4 are in μg/Kg weight of the individuals (i.e., animals). Del Soldato further teaches that said compounds are administered in the pharmaceutical formulations according to the methods well known in the art (e.g., Remington's Pharmaceutical Sciences, 15 th Edition). Remington's Pharmaceutical Sciences is a compendium that teaches all forms of pharmaceutical preparations in any shape, form or types of dosage and methods to administer said dosage Thus, the prior art explicitly and inherently teaches the claimed method Thus, the reference discloses a method encompassing the pharmaceutical preparations that appear to be identical to the presently claimed compound.

Therefore, the reference is deemed to anticipate the cited claims.

However, even if the reference method and the pharmaceutical compositions, preparations and diseases being treated via administering said compounds according to the method steps being taught in the prior art reference and the claimed method are not one and the same and there is, in fact, no anticipation, the reference method comprising administering of same compounds, to treat same diseases; nevertheless, have rendered the claimed method obvious to one of ordinary skill in the art at the time the claimed invention was made in view of the fact that the reference discloses that same compounds in same pharmaceutical excipient and carriers as well as compositions are administered to treat the same diseases as that claimed were known. Thus, the claimed invention as a whole was clearly *prima facie* obvious especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claim Rejections Under 35 U.S.C. § 103(a)

21. Claims 1-10 and 21-22 are rejected under 35 U.S.C. §103 (a) as obvious over combined teachings from Del Soldato (WO 99/00361) that is equivalent of Del Soldato (U.S. Patent 218, 417 B1). In this rejection U.S. Patent 218, 417 B1 is discussed, in view of Chobanian et al (U. S. Patent 5,645,839)

Claims recite "a method to treat a vascular disease characterized by nitric oxide insufficiency in a patient" via administering to said patient a "therapeutically effective amount of at least one nitrosated angiotensin converting enzyme inhibitor" (i.e., NACEI), "wherein one of the vascular disease is a cardiovascular disease among hypertension, congestive heart failure, myocardial infarction, artheriosclerosis or like. Said NACEI further comprises a pharmaceutical acceptable carrier and may also be a salt of a NACEI. Said NACEI is administered in a solid dose form of a capsule or tablet, wherein said tablet or capsule is a sustained release capsule or tablet.

Regarding Claims 1-10 and 21-22, teachings from Del Soldato have already been discussed *supra.* Del Soldato's teachings, however, do not explicitly show instantly claimed limitation of a sustained release solid pharmaceutical dosage. Chobanian et al. while teaching methods and compositions to treat a variety of disease encompassing cardiovascular diseases, hypertension, heart failure and the like via administering angiotensin inhibitors in combination with nitrosated compounds (Column 1, Lines 7-32), wherein said angiotensin inhibitor comprises an angiotensin converting enzyme inhibitor and a pharmaceutically acceptable excipient (Column 3, Lines 40-58 and Lines 64-67) is administered to a patient in form of coated tablets or capsules (Column 5, Lines 35-37; Claims 1-3,and 5-6)). Since sustained release preparation by definition are "A way of formulating a medicine so that it is released into the body steadily, over a long period of time, thus reducing the dosing frequency (See www.ardana.co.uk/glossary.html), Chobanian et al. explicitly teach a composition comprising a

pharmaceutically accepted carrier and an angiotensin inhibitor and intrinsically said composition is a sustain release oral composition according to the art–accepted definition of a sustained release dosage.

Thus, at the time, the claimed invention was made, an artisan of ordinary skill would have been motivated to combine the teachings from Del Soldato according to beneficial teachings from Chobanian et al. to obtain a method to treat a nitric oxide insufficiency mediated vascular disease, wherein said disease is a cardiovascular disease among congestive heart failure, hypertension etc .via administering a composition comprising at least one nitrosated angiotensin converting enzyme inhibitor in a pharmaceutically acceptable carrier as a sustained release oral solid dosage because Del Soldato teaches to treat a vascular/cardiovascular disease through administering at least one nitrosated angiotensin converting enzyme inhibitor in a pharmaceutically acceptable carrier as an oral solid dosage and Chobanian et al. while teaching treatment of cardiovascular/vascular diseases with a composition comprising a pharmaceutically acceptable carrier in a oral solid dosage also teach that said oral dosage is a sustained release oral dose.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify teachings from Del Soldato according to beneficial teachings from Chobanian et al. to obtain a method to treat a nitric oxide insufficiency mediated disease via administering a composition comprising at least one nitrosated angiotensin converting enzyme inhibitor wherein said disease e.g., is a cardiovascular disease among congestive heart failure, hypertension as discussed *supra*. Thus, the cited references clearly show that at the time of the invention, a method to treat cardiovascular disease by administering a composition comprising a nitrosated angiotensin converting enzyme inhibitor in a pharmaceutically accepted carrier was available. It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose. The idea for combining them flows logically from their having been used individually in the prior art. *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960).

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

CONCLUSION

22. For the aforementioned reasons, no claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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24 March 2007

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